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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,034	09/09/2003	Hiroaki Shizuya	CIT1620-1	3294

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DLA PIPER US LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
LI, QIAN JANICE	

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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,034	SHIZUYA, HIROAKI	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-14,16-19,21-25,27-41 and 43-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-14, 16-19, 21-25, 27-41, 43-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/14/07 has been entered.

Claims 1, 45, 46 have been amended. Claims 1, 3-14, 16-19, 21-25, 27-41, 43-52 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. Upon further search and consideration, new grounds of rejections are necessitated and appear below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-14, 16-19, 21-25, 27-41, 43-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the amendment introduces an intermediate and a third construct, it is unclear how the intermediate construct differs from the second construct, and what is the content of the third construct, what kind of mouse DNA it contains, how it differs from the first construct, and thus the metes and bounds of the claims are uncertain.

Claim 7 recites the limitation "the *E coli*" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology

Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 41 is rejected under 35 U.S.C. 102(b) as being anticipated by *Shiao et al* (Transgenic Res 1999;8:295-302).

Shiao et al teach a transgenic mouse whose genome comprising a genetic construct containing a human glucagon receptor (GR) gene flanked by a first and second mouse DNA sequence orthologous to and have the same order and orientation relative to the human GR gene DNA sequence (See e.g. column 1, page 296, and figure 1a). To the extend that the GR gene is a metabolic pathway gene, involved in glycolysis metabolic process, the mouse disclosed by *Shiao et al* anticipate instant claims. Note the specification teaches, "Examples of metabolic pathways include, but are not limited to glycolysis and the Kreb's cycle" (Specification, paragraph 0072).

It is noted that the prior art mouse differs from the instantly claimed mouse only by their method of manufacture. However, patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

Accordingly, *Shiao et al* anticipate instant claim.

Claims 41, 47, 49, 50-52 are rejected under 35 U.S.C. 102(b) as being anticipated by *Divoky et al.* (Proc. Natl. Acad. Sci. USA 98(3): 986-991, 30 Jan. 2001).

Divoky discloses a DNA construct for performing homologous recombination in an ES cell, and a transgenic mouse made from the ES cell. The construct comprises the coding region of the human erythropoietin receptor gene (EPOR) from the start codon to the stop codon flanked by first and second mouse genomic DNA sequences. The first mouse DNA sequence is approximately 7 kb of genomic sequence upstream from the start codon of the mouse EPOR gene, and the second mouse DNA sequence is approximately 5 kb downstream from the stop codon of the mouse EPOR gene, i.e. the portion of the mouse EPOR gene from the start to stop codons has been replaced with its human ortholog. The human EPOR coding sequence comprises a positive selection marker expression cassette (*flox-neo*), inserted within an intron. The recombination events were detected by Southern blotting with an *Eco*RV-*Sal*I 5' probe and *Xba*I-*Eco*RV 3' probe, and thus these RE sites are considered as a second selection marker adjacent to one of the non-human DNA sequences. The DAN construct was used to replace the mouse EPOR coding sequence in one copy of the EPOR gene in a mouse ES cell. These ES cells were then implanted into mouse blastocysts, which were implanted into a pseudopregnant mouse to produce a chimeric "humanized" mice which were then bred to produce transgenic humanized mice carrying one or two copies of the human EPOR

coding sequence in place of the orthologous mouse EPOR coding sequence. See page 986, col. 2, through page 987, col. 1; page 987, col. 2; Fig. 1, page 988). To the extent that EPOR is a cell surface receptor involved in the cell-signaling pathway, it meets the limitations of claim 41. Note the specification defines, "Cell-signaling systems may include, but are not limited to cell-surface and intracellular receptor proteins..." (Specification, paragraph 0076).

The DNA construct of *Divoky* was constructed *in vitro* using PCR, restriction enzymes, and DNA ligase, rather than by recombination as required in instant claims 1, 3-14, 16, 17, 25, and 27-40. However, the method of making could not distinguish the DNA construct used by *Divoky* or instantly claimed, and the resulting mouse made using such a construct would be the same.

Accordingly, *Divoky et al* anticipate instant claims.

Claim Rejections - 35 USC § 102/103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8, 16, 17, 25, 32, 34, 39, 40, 45, 46 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Shiao et al* (Transgenic Res 1999;8:295-302).

Shiao et al teach a method of making a humanized transgenic mouse whose genome comprising a genetic construct comprising a human glucagon receptor (GR) gene flanked by a first and second mouse DNA sequence orthologous to and have the same order and orientation relative to human DNA sequence. *Shiao et al* teach the design of the GR replacement vector to include the murine 5' flanking region fused with the entire human GR gene at the common start condon site so that the expression of the human GR gene was under the control of the mouse promoter and expressed in a tissue specific manner (column 2, page 298). *Shiao et al* go on to teach to include the 3' flanking sequence from the mouse GR gene to promote efficient targeting (allows for recombination).

Although *Shiao et al* do not specify a first, second, third, and fourth constructs as instantly recited, since the recited "recombining" embraces any means (such as the enzymatic method taught by *Shiao et al*), and numerous steps of recombining leading to the construction of a final targeting vector, and since the process of making the final genetic construct as taught by *Shiao et al* comprise a serial of steps and constructs which could have been considered as the first, second, third, and the final (fourth) constructs before it is introduced to the mouse ES cells.

Accordingly, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated, by the references, in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 1, 3, 8, 10, 11, 13, 14, 16, 17, 25, 27, 32, 34, 35, 37, 39, 40, 45 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Divoky et al.* (Proc. Natl. Acad. Sci. USA 98(3): 986-991, 30 Jan. 2001).

Divoky discloses a series of constructs and steps of making a final DNA construct for performing homologous recombination in a mouse ES cell, and a transgenic mouse made from the ES cell. The initial mouse genomic sequence is carried by a bacterial artificial chromosome (BAC, e.g. column 2, page 986). The construct was detailed *supra*. The DAN construct was used to replace the mouse EPOR coding sequence in one copy of the EPOR gene in a mouse ES cell. These ES cells were then implanted into mouse blastocysts, which was implanted into a pseudopregnant mouse to produce a chimeric "humanized" mice which were then bred to produce transgenic humanized mice carrying one or two copies of the human EPOR coding sequence in place of the orthologous mouse EPOR coding sequence. See page 986, col. 2, through page 987, col. 1; page 987, col. 2; Fig. 1, page 988).

Although *Divoky et al* do not specify a first, second, third, and fourth constructs as instantly recited, since the recited "recombining" embraces any means (such as the enzymatic method taught by *Divoky et al*), and numerous steps of recombining leading to the construction of a final targeting vector, and since the process of making the final genetic construct as taught by *Divoky et al* comprise a serial of steps and constructs which could have been considered as

the first, second, third, and the final (fourth) constructs before it is introduced to the mouse ES cells.

Accordingly, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated, by the references, in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 4-7, 9,12, 18, 19, 21-24, 28-31, 33, 36, 38, 41, 47, 48 are rejected under 35 U.S.C. 103(a) as being obvious over *Divoky et al.* (Proc. Natl. Acad. Sci. USA 98(3): 986-991, 30 Jan. 2001) in view of *Heintz et al* (Nat Rev 2001;2:861-70), and as evidenced by (*Chrast et al*, Transgenic Res 1999 Apr;8:147-50).

The teaching of the *Divoky et al* differs from instant claims in that they did not use a BAC targeting construct and *E coli* in all steps of the recombining process.

Heintz et al supplemented the deficiency by establishing that at the time of instant filing date, that BAC has become the choice of vehicles for genome analysis, and making targeting vectors to generate transgenic mouse. Compared to other conventional vectors such as YACs, BACs are simple to prepare and manipulate, can carry several hundred kilobases of DNA, propagated at low copy number, and more stable (e.g. box 1). *Heintz et al* teach the use of reporter genes and targeted-expression have been crucial in the analysis of gene expression and function in many studies including making transgenic animals, but limited in mammalian studies by the intrinsic difficulty of identifying key

regulatory elements and large genome manipulation. *Heintz et al* teach the F-factor-based bacterial artificial chromosomes provide a tool that took advantage of the precision of homologous recombination in recombination-deficient strain of *E. coli* (such as a recA mutation, claim 7), which had been used extensively for marker insertion into, and excision from the bacterial genome (e.g. box 1). *Heintz et al* review technical aspects regarding how the BAC works for making target vectors by homologous recombination in the recombination-deficient strain of *E. coli*: a) restoring the capability of homologouse recombination of the BAC by the reintroduction of the *E. coli recA* gene, for example; b) targeting the desired modification cassette into a precise site on the genomic DNA insert using a shuttle vector that carries the desired reporter gene or modification cassette, flanked by sequences homologous to the genomic DNA carried in the BAC; c). using positive and negative selection markers to select correct recombination, to enrich the desired end-product, i.e. a BAC that carries the modification cassette inserted into the exact position chosen in the design of the experiment (e.g. column 1, page 862). *Heintz et al* go on to teach multiple recombination steps might be necessary for resolution or excision. *Heintz et al* also teach the BAC system has been successfully used to insert reporter genes into large segment of CNS-expressed genes and BAC transgenic mice have been made (column 2, page 862).

As to the linearized BAC, it is a mid-product during BAC preparation (*Chrast et al*).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method taught by *Heintz et al,* for making the targeting vector as taught by *Divoky et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the advantage of the BAC system as taught by *Heintz et al.* Given the success in the art for making BAC transgenic mouse, one would have had a reasonable expectation of success for inserting any human/animal gene of interest into a mouse/another animal genome. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Divoky et al.* (Proc. Natl. Acad. Sci. USA 2001;98(3): 986-991) in view of *Heintz et al* (Nat Rev 2001;2:861-70) as applied to claims 4-7, 9,12, 18, 19, 21-24, 28-31, 33, 36, 38, 41, 47, 48 above, and further in view of *Xie et al* (Nature 2000;406:435-9, IDS).

Claims 43 and 44 are directed to a transgenic mouse whose genome comprising a human drug metabolism gene such as PXR. The combined teaching of *Divoky et al* in view of *Heintz et al* as discussed supra does not specify such a gene. However, given the general applicability of the method taught by *Heintz et al,* for making a transgenic animal, and the desirability for making a humanized xenobiotic response in a mouse model as taught by Xie et al, it would have been obvious to one of ordinary skill in the art to apply the

method taught by *Heintz et al,* for making a mouse model having a humanized xenobiotic response as taught by *Xie et al* with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of

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Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
June 14, 2007